REMARKS

Applicant respectfully requests entry of the foregoing and continued examination of the subject matter identified in caption, as amended, pursuant to and consistent with 37 C.F.R. § 1.114, and in light of the remarks which follow.

Claims 1-5, 7-9 and 11-12 are currently pending. Applicants note with appreciation that the rejection of claim 2 under 35 U.S.C. § 112, second paragraph, and the objection to claim 4 have been overcome.

Claims 1, 2, 3, 4 and 7 are amended herein. Claims 13 and 14 are added. Basis for these amendments and new claims may be found throughout the specification and claims as-filed, especially at page 2, lines 7-19 and lines 24-27, as well as page 3 line 13 to page 4, line 2. Thus, no prohibited new matter is presented by way of the present Amendment. Applicants reserve the right to file at least one continuation or divisional application directed to any subject matter canceled by way of the present Amendment.

Rejections Under 35 U.S.C. § 103

Claims 1-4 and 7-12 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Sui et al. (*PNAS*, Vol. 92 (1995)) and further in view of Wong et al. (WO 96/04314). Sui et al. is cited for purportedly disclosing the administration of a IL-6/IL-6R complex. Wong et al. is cited for purportedly disclosing that it is advantageous to make fusion proteins. The Office Action states that it would have been *prima facie* obvious to the skilled artisan to make a fusion protein, as disclosed by Wong et al., comprising IL-6 and IL-6R, because administration of a IL-6/IL-6R complex along with SCF increases expansion of progenitor cells, as disclosed by Sui et al. Applicants respectfully traverse.

As set forth in M.P.E.P § 2142, in order to establish a prima facie case of obviousness, three criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art references must teach or suggest all the claim limitations. Applicants

submit that these criteria are not met by the cited references, alone or in combination.

Before turning to the cited references, Applicants note that the claims are amended herein to recite a fusion polypeptide comprising a first and second polypeptide, the polypeptides having an affinity with respect to each other. The first polypeptide is a cytokine of the interleukin-6 family, or subunit thereof, and the second polypeptide is a receptor that binds to the first polypeptide. The first and second polypeptides are linked to each other via a polypeptide linker.

No motivation to combine or modify the cited references.

Turning to the cited references, Sui et al. discloses that a combination of IL-6 and IL-6R in the presence of SCF is a stimulator for the proliferation of human primitive hemopoietic progenitors. Sui et al. further discloses that no other cytokine has been reported to have such a synergy with SCF in the stimulation of human primitive hemopoietic cells. As such, Sui et al. discloses an *in vitro* expansion of hemopoietic cells to prepare suitable hemopoietic cells for potential clinical application, including gene therapy. Sui et al. states that the combination of IL-6 and IL-6R functions only in the presence of SCF, as revealed in the present study. To perform the study in Sui et al., normal human $CD34^+$ cells were isolated from cord blood and cultured with IL-6 and IL-6R in the presence of SCF.

Applicants respectfully submit that Sui et al. does not disclose or suggest the administration of a fusion polypeptide comprising a first and second polypeptide, the polypeptides having an affinity with respect to each other, wherein the first polypeptide is a cytokine of the interleukin-6 family, or subunit thereof, and the second polypeptide is a receptor that binds to the first polypeptide and the first and second polypeptides are linked to each other via a polypeptide linker.

Wong et al. relates to novel complexes of major histocompatability complex (MHC) molecules. Wong et al. discloses MHC fusion complexes containing an MHC molecule with a petide-binding groove and a presenting peptide covalently linked to the MHC protein. Wong et al. discloses that a "presenting peptide" refers to a peptide that is capable of modulating the activity of a T cell receptor and Wong et al.

discloses that covalently linking the presenting peptide to the MHC peptide provides a number of advantages with regard to interaction with T cell receptors. Wong et al. further discloses that the MHC fusion complexes are useful for in vitro screens for identification and isolation of peptides that modulate activity of selected T cells, including peptides that are T cell receptor antagonists and partial antagonists, methods of suppressing an immune response in a mammal and methods for inducing an immune response in a mammal.

Applicants respectfully submit that Wong et al. specifically relates to MHC fusion complexes and the advantages thereof with regard to interaction with T cell receptors. Applicants further respectfully submit that the MHC fusion complexes of Wong are signficantly different than the presently claimed fusion polypeptides comprising a first and second polypeptide, wherein the first polypeptide is a cytokine of the interleukin-6 family, or subunit thereof, and the second polypeptide is a receptor that binds to the first polypeptide. Wong does not in any way disclose, suggest, or relate to a cytokine or a cytokine receptor or activity related thereto.

In contrast, the presently claimed invention relates to a fusion polypeptide comprising a first and second polypeptide, the polypeptides having an affinity with respect to each other, wherein the first polypeptide is a cytokine of the interleukin-6 family, or subunit thereof, and the second polypeptide is a receptor that binds to the first polypeptide and the first and second polypeptides are linked to each other via a polypeptide linker. The presently claimed fusion polypeptide is useful in remedying unbalanced interactions between proteins. Applicants respectfully submit that the skilled artisan would not be motivated to use Sui et. al. combined with Wong et al. in an attempt to achieve the benefits of the presently claimed fusion polypeptides.

No reasonable expectation of success.

Accordingy, Applicants respectfully submit that there is no suggestion or motivation, either in Sui et al. or Wong et al. or in the knowledge generally available to one of ordinary skill in the art, to modify Sui et al. or to combine the teachings of Sui et al. and Wong et al. As explained in MPEP § 2143.01, the mere fact that references can be combined or modified does not render the resultant combination

obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

As described above, Sui et al. disclose that a combination of IL-6 and IL-6R in the presence of SCF is a stimulator for the proliferation of human primitive hemopoietic progenitors. As such, Sui et al. merely discloses an *in vitro* expansion of hemopoietic cells cultured with IL-6 and IL-6R in the presence of SCF. Sui et al. state that the results obtained indicated that the combination of SCF, IL-6, and IL-6R is a potent stimulator and exhibits striking synergy. Accordingly, Sui et al. provide no motivation to alter the combination of SCF, IL-6, and IL-6R as set forth therein.

Moreover, as described above, Wong et al. merely relates to MHC fusion complexes containing an MHC molecule with a peptide-binding groove and a presenting peptide covalently linked to the MHC protein, and the advantages thereof with regard to interaction with T cell receptors. As such, Wong describes the activation of T cells via a complex from a surface protein of a cell, *i.e.*, a MHC molecule, and a peptide to be presented. No receptor in Wong is fused with the corresponding cytokine. As such, Applicants respectfully submit that the MHC fusion complexes of Wong are significantly different than the presently claimed fusion polypeptides and are significantly different than the combination of SCF, IL-6, and IL-6R of Sui et al. Wong does not in any way disclose, suggest, or relate to a cytokine or a cytokine receptor or activity related thereto.

Applicants respectfully submit that the present art of fusion polypeptides is quite complex, and a skilled artisan would not be lead to extrapolate from the benefits of Wong with regard to MHC fusion complexes and modulation of T cell activity to the combination of Sui et al. of SCF, IL-6, and IL-6R. Therefore, Applicants respectfully submit that there is no suggestion or motivation, either in Sui et al. or Wong et al. or in the knowledge generally available to one of ordinary skill in the art, to modify Sui et al. or to combine the teachings of Sui et al. and Wong et al.

Do not disclose or suggest each claimed element.

Applicants further respectfully submit that even if there were some suggestion or motivation to combine the teachings of Sui et al. and Wong et al, there is no reasonable expectation of success in doing so. As described above, Sui et al.

disclose a combination of IL-6 and IL-6R in the presence of SCF that is a potent stimulator for the proliferation of human primitive hemopoietic progenitors and that exhibits striking synergy. Also as described above, Wong et al. relate to MHC fusion complexes and the advantages thereof with regard to interaction with T cell receptors. The MHC fusion complexes of Wong are significantly different than the presently claimed fusion polypeptides and are also significantly different than the combination of SCF, IL-6, and IL-6R of Sui et al.

As the MHC fusion complexes of Wong et al. and the combination of SCF, IL-6, and IL-6R of Sui et al. are significantly different and the present art of fusion polypeptides is quite complex, Applicants respectfully submit that a skilled artisan would have no reasonable expectation of success in combining the teachings of Sui et al. and Wong et al.

Applicants further respectfully submitted that even if there were some suggestion or motivation to combine the reference teachings and a reasonable expectation of success, the cited art references when combined do not disclose or suggest all the claim limitations. Even when combined, Sui et al. and Wong et al. do not disclose or suggest all of the claim limitations of the fusion polypeptide. The combination of Sui et al. and Wong et al. does not disclose or suggest the presently claimed fusion polypeptide comprising a first and second polypeptide, the polypeptides having an affinity with respect to each other, wherein the first polypeptide is a cytokine of the interleukin-6 family, or subunit thereof, and the second polypeptide is a receptor that binds to the first polypeptide and the first and second polypeptides are linked to each other via a polypeptide linker.

As set forth in the specification, for the present invention the separate application of IL-6 and its receptor is disadvantageous and is a problem addressed by the present invention. The presently claimed fusion polypeptide has been found to have significant advantages. The particular fusion polypeptide of the present invention has been found to greatly increase the effects of the individual polypeptides. As set forth in Example 5 of the specification, the expansion and colony formation of $CD34^+$ cells can be increased by 300% as compared to the separate administration of IL-6 and the IL-6 receptor. As set forth in Example 4 of

the present specification, the claimed fusion polypeptide further stimulates haptoglobin expression many times over as compared with to the separate addition of IL-6 and the IL-6 receptor, thus influencing liver cells to regenerate. In fact, the fusion peptide of the present invention can result in the complete regeneration of diseased liver tissue.

The fusion polypeptides of the present invention are able to successfully influence and reduce harmful protein interactions, resulting in benefits such as the regeneration of diseased liver tissue. As previously provided with the Reply and Amendment of May 24, 2002, by way of support of the above Applicants again refer to U.S. Patent No. 5,919,763 ("Rose-John") and Galun (*FASEB J.* (2000) 14:197), Hecht (*Mol. Therap.* (2001) 3:638-87), as well as Pflanz (*FEBS Letters* (1999) 450:117-22) and März (*Eur. J. Neurosci.*). These references show conjugates from IL-11 and the IL-11 receptor or CNTF and the CNTF receptor and their effect on liver cells (Pflanz) or neuronal cells (März) (*see also* present specification, page 2).

Applicants further submit herewith Fischer (Nature Biotech. (1997) 15: 142-45). Fischer discloses the use of H-IL-6 (linked with sIL-6R) as useful for the expansion of human hemopoietic progenitor cells, in comparison with the administration of unlinked IL-6 and sIL-6R. Applicants note that the present fusion polypeptide of the claimed invention is fully active at a100 to 1000-fold lower concentration that the combination of unlinked IL-6 and sIL-6R. This result is not only surprising and unexpected, but it is also extremely beneficial to the therapeutic use of the present invention. Only the fusion polypeptide of IL-6 and IL-6R can regenerate diseased liver tissue, and not the unlinked IL-6 and IL-6R. These benefits are not at all disclosed by the cited references.

Applicants submit that the fusion polypeptide of the present invention provides a new group of compounds which surprisingly eliminate any disturbed interaction between proteins.

For at least the above-described reasons, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this Amendment, or the application in general, the Examiner is respectfully requested to telephone the undersigned attorney so that prosecution of the application may be expedited.

Respectfully submitted,

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